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Nome e Cognome Autore, Nome e Cognome Autore

Introduzione di nuove tecnologie nei programmi di screening del cancro

Aspetti metodologici

HTA Eunethta –

HTA Core Model DOMAINS

1. Health problem and current use of technology
2. Description and technical characteristics
3. Safety
4. Clinical effectiveness
5. *Costs and economic evaluation*
6. *Ethical analysis*
7. *Organisational aspects*
8. *Social aspects*
9. *Legal aspects*

Nuove tecnologie per lo Screening del cancro: scenari

1. Programma di screening efficace, raccomandato
2. Programma di screening efficace, non raccomandato
3. Programma di screening in fase di valutazione di efficacia
4. Progetto di ricerca per programma di screening

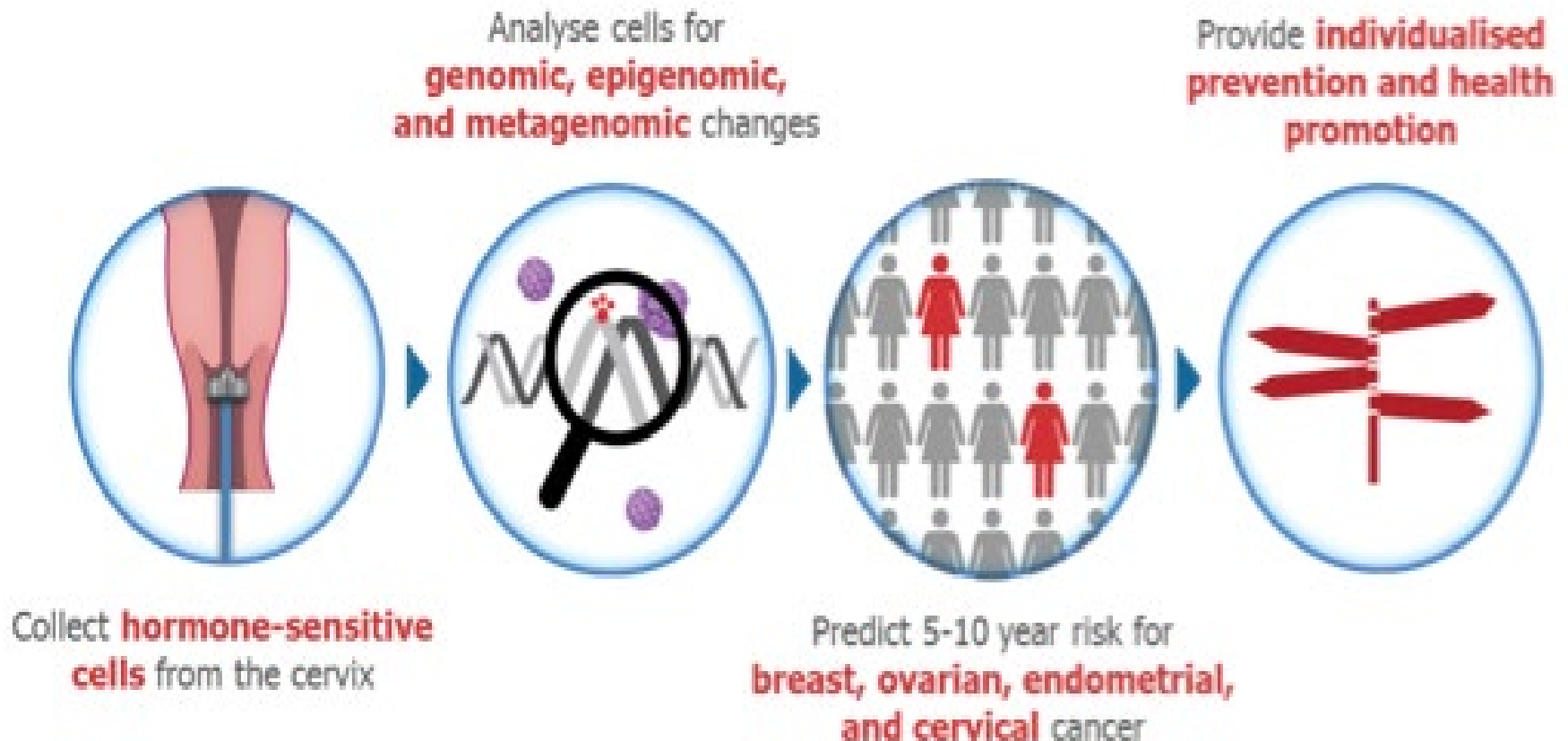
Nuove tecnologie di screening:

- **Programma**
- **Protocollo**
- **Test**

Nuova tecnologia di screening

NT	Disegno dello studio (pre introduzione)	Outcome principale	Durata f.u.
Programma	RCT prospettico	Mortalità incidenza	10-20 anni
Protocollo	RCT trasversale, longitudinale breve	Detection Rate Casi intervallo	1, 2-5 anni
Test	Trial accuratezza diagnostica	Concordanza diagnostica, VP, Detection Rate, Casi intervallo	1, 2-5 anni

“The **FORECEE research project** is a unique investigation of the molecular and bacterial/viral factors that may predict a woman’s risk of developing breast, ovarian, endometrial and cervical cancer (the 4Cs).”



es Programma

3/4 anno 36
maggio
agosto
2012

**EPIDEMIOLOGIA
& PREVENZIONE**

Rivista dell'Associazione italiana di epidemiologia



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HTA REPORT

HEALTH TECHNOLOGY ASSESSMENT

RICERCA DEL DNA DI PAPILLOMAVIRUS UMANO (HPV) COME TEST PRIMARIO PER LO SCREENING DEI PRECURSORI DEL CANCRO DEL COLLO UTERINO

HPV-DNA-BASED PRIMARY SCREENING FOR CERVICAL CANCER PRECURSORS



Ronco G, Accetta G,
Angeloni C, Arbyn M,
Barzon L, Biggeri A, Calvia M,
Capoluongo E, Carozzi F,
Cogo C, Confortini M,
Cuzick J, Federici A, Frega A,
Ghiringhello B, Gillio Tos A,
Giordano L, Maioli P,
Mejier C, Naldoni C,
Napoletano F, Perego D,
Rabino V, Ribaldone R,
Sapino A, Segnan N,
Sideri M, Snijders P, Sotis C,
Surico N, Zappa M, Zorzi M,
Giorgi Rossi P

Organizzazione

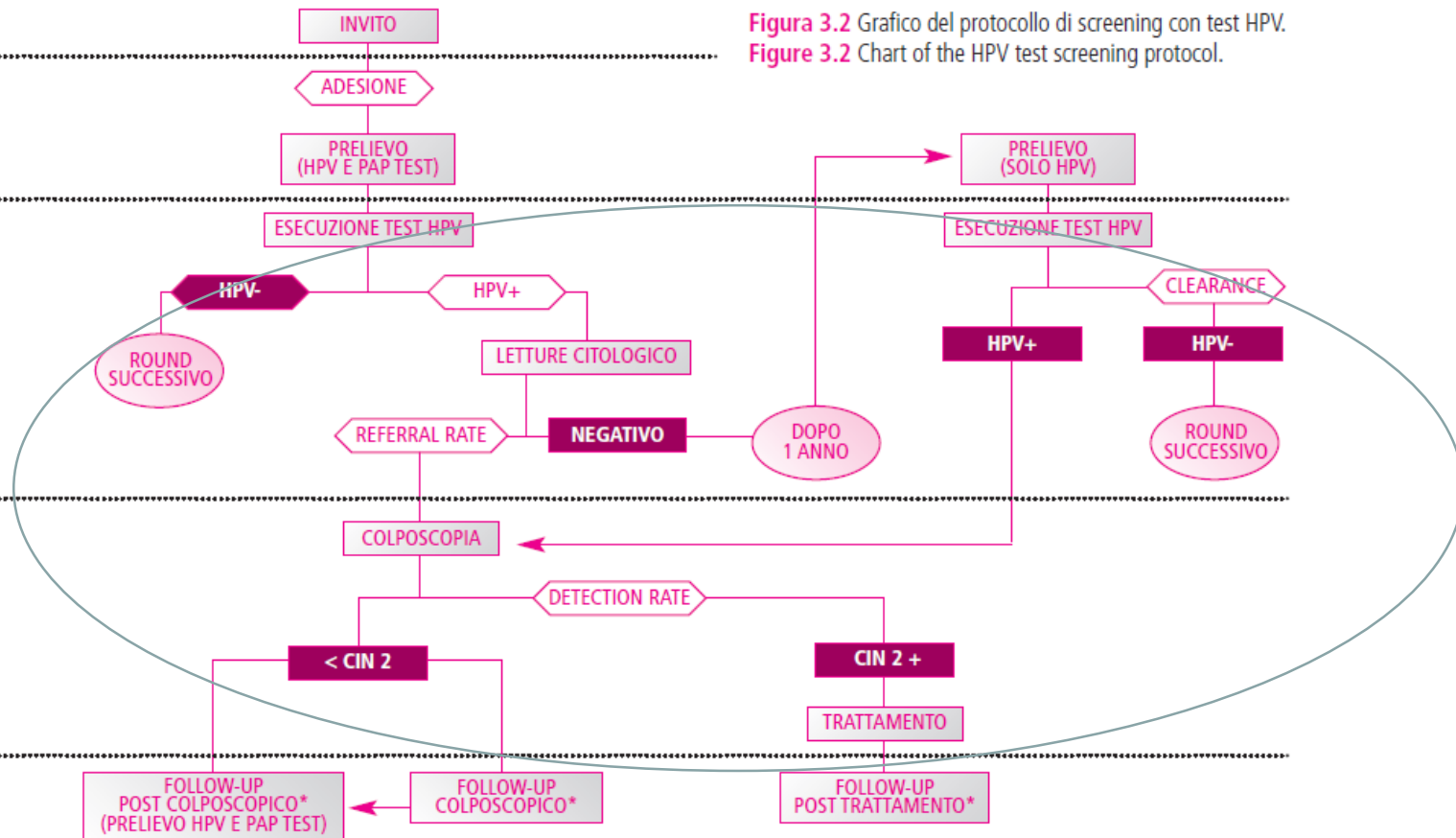
Primo livello

Laboratorio

Secondo livello

Follow Up

Figura 3.2 Grafico del protocollo di screening con test HPV.
Figure 3.2 Chart of the HPV test screening protocol.



*Per agevolare la comprensibilità del grafico, si è preferito non specificare la suddivisione del follow-up tra indagini colposcopiche e prelievi citologici; se ne è, invece, tenuto conto nel calcolo dei costi.

Rapporti HTA su screening del cervicocarcinoma. Epidemiol Prev 2012; 36 (5) Raccolta

es protocollo

Rotterdam screening trial in 15.013 average risk screening-naïve individuals aged 50 – 74 years

	% Adherence	% positive test	% true positives*	True positives per 1000 invited
gFOBT	50	2.8	45	6
FIT ⁵⁰	62	8.1	42	21
Sigmoidoscopy	32	10.2	100	33
2-step: Sigmo + FIT ⁵⁰	57	16.8		43

** of those with positive test*

Es. test

Numbers needed to screen and scope to detect one screennee with an advanced neoplastic lesion

	NN Screen	NN Scope
gFOBT	84	2.2
FIT⁵⁰	31	2.4
FIT⁷⁵	37	2.0
FIT¹⁰⁰	41	1.9
FIT¹²⁵	43	1.8
FIT¹⁵⁰	44	1.7
FIT¹⁷⁵	46	1.6
FIT²⁰⁰	49	1.6

Outcome

- Riduzione mortalità
- Riduzione mortalità e incidenza

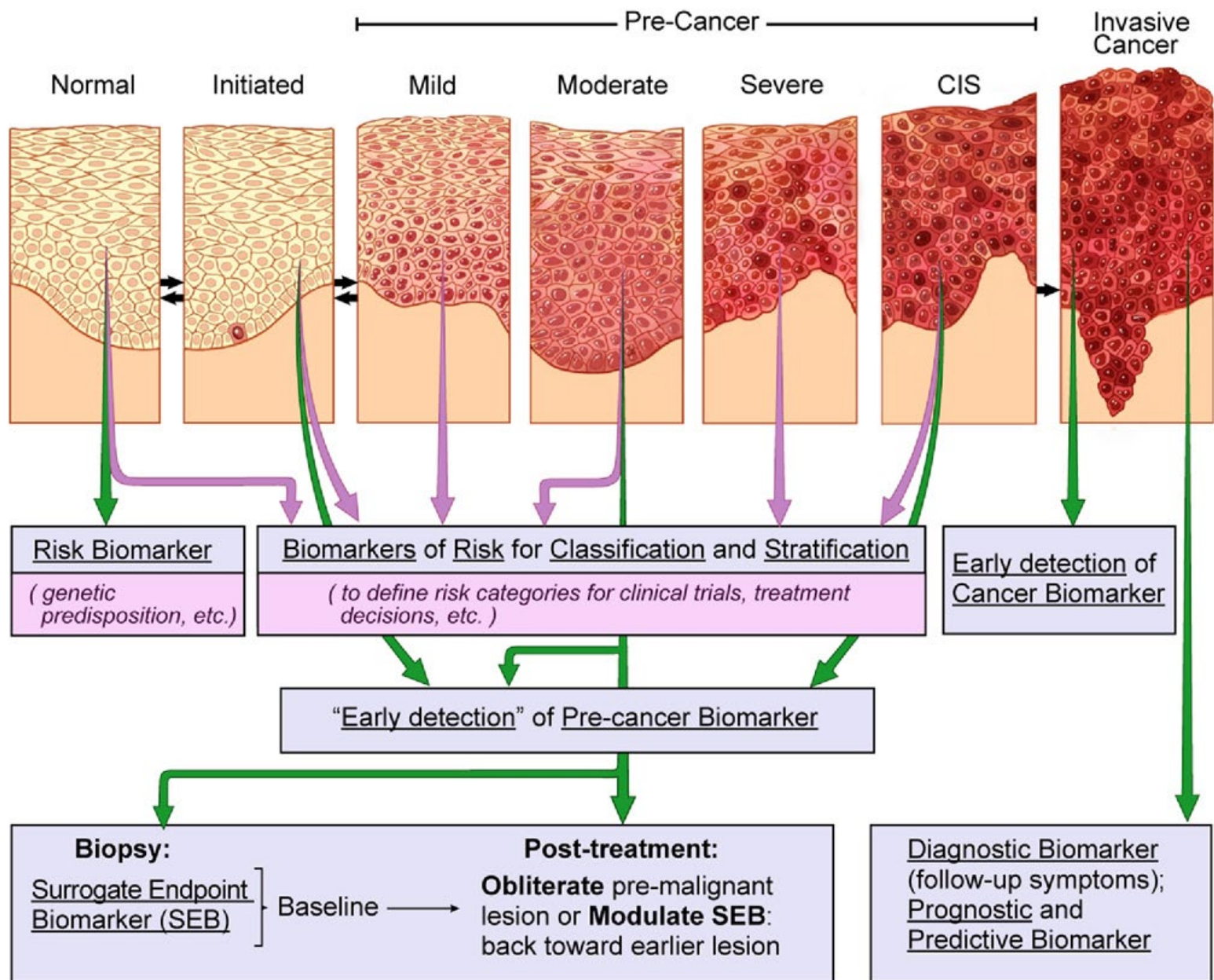


TABLE 1. Estimates of CRC ADP in 3 Randomized Controlled Trials of Flexible Sigmoidoscopy Screening

		Intervention Group				Control Group			Averted Events			
		Total	Cancers (Ci)	Deaths (Di)	Total	Cancers (Cc)	Deaths (Dc)	Fatality Rate (FRc)	Cancers ^a	Deaths ^b	ADP ^c	ADP % ^d
		No.	No.	No.	No.	No.	No.	Percentage, (95% CI)	No.	No.	No.	Percentage, (95% CI)
ITT	PLCO 2017 ⁶	77,445	1008	253	77,445	1291	351	27 (25-30)	283	98	77	79 (69-86)
	SCORE 2011 ³	17,136	251	65	17,136	306	83	27 (22-32)	55	18	15	83 (59-96)
	UK Flexible Sigmoidoscopy Screening Trial 2010 ¹	57,099	706	189	112,939	1818	538	30 (27-32)	422	164	125	76 (69-82)
	UK Flexible Sigmoidoscopy Screening Trial 2017 ^{2e}	57,098	1230	353	112,936	3253	996	31 (29-32)	820	298	251	84 (80-88)
PP	SCORE 2011 ³	9911	126	33	17,136	306	83	27 (22-32)	88	26	24	92 (75-99)
	UK Flexible Sigmoidoscopy Screening Trial 2010 ¹	40,621	445	111	112,939	1818	538	30 (27-32)	581	229	172	75 (69-81)
	UK Flexible Sigmoidoscopy Screening Trial 2017 ^{2e}	40,621	776	215	112,936	3253	996	31 (29-32)	1096	398	335	84 (80-88)

Abbreviations: 95% CI, 95% confidence interval; ADP, averted deaths due to prevention; Cc, cancers in the control group; Ci, cancers in the intervention group; Dc, deaths in the control group; Di, deaths in the intervention group; FRc, fatality rate in the control group; ITT, intention-to-treat analysis; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PP, per-protocol analysis; UK, United Kingdom.

^a Estimated as the difference between the Cc and the Ci, which was estimated assuming a control:intervention population ratio of 1:1.

^b Estimated as the difference between the Dc and the Di, which was estimated assuming a control:intervention population ratio of 1:1.

^c Estimated as the product of fatality rate per the averted cancers: $(Cc - Ci) * (Dc / Cc)$.

^d Estimated as the ratio between the prevented deaths and the averted deaths. The complete algorithm is: $ADP \% = ((Cc - Ci) * (Dc / Cc)) / (Dc - Di)$.

^e UK Flexible Sigmoidoscopy Screening Trial 2017 reports results after 17 years of follow-up versus 10.5 to 11.9 years for the other randomized controlled trials.

main factors can improve the point estimate of survival in the intervention arm, namely: 1) better access to treatment that would increase survival; it most likely is not the case because the intervention and usual-care arms of the PLCO trial were sampled within the same health maintenance organizations; 2) overdiagnosis, which is intrinsic to cancer screening; and 3) the sensitivity of the test and the compliance with screening, affecting the percentage of screen-detected cancers.

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Averted Events

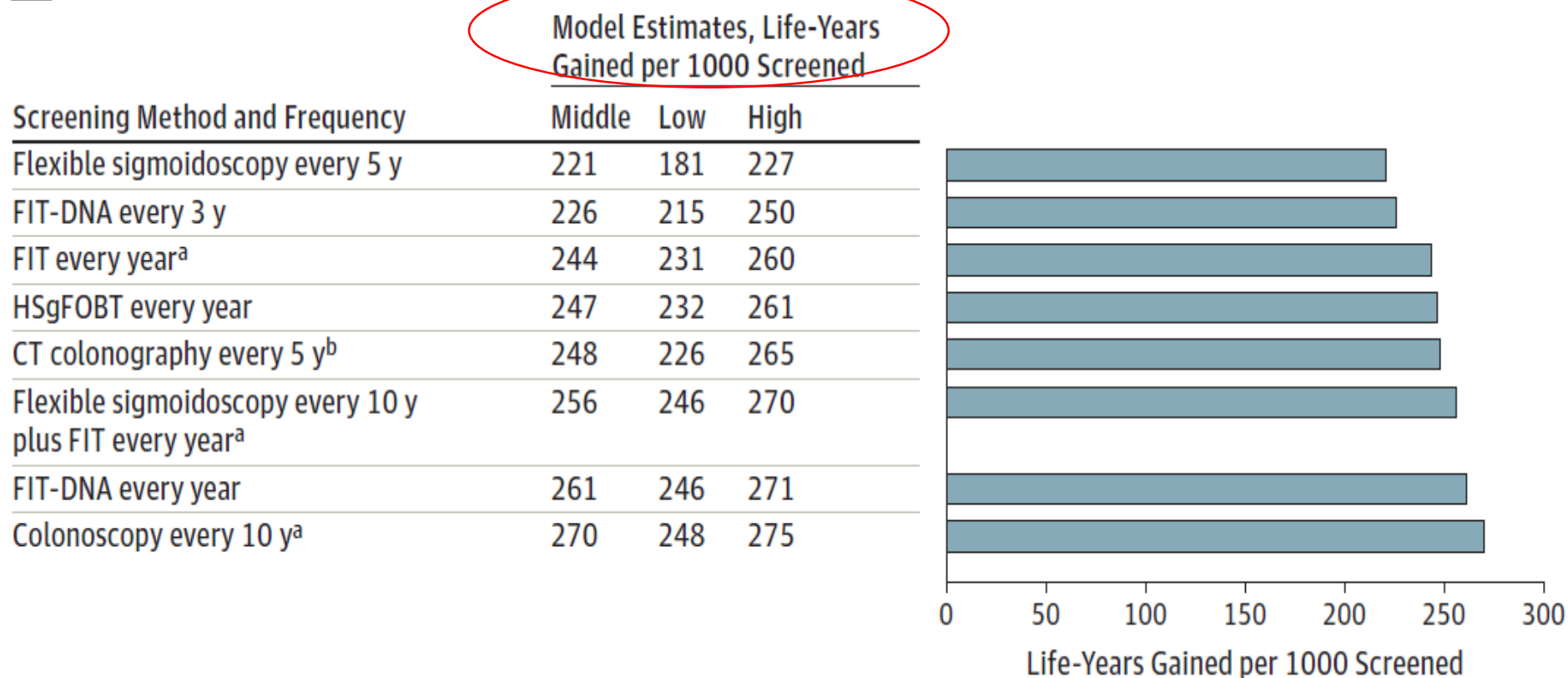
Cancers ^a	Deaths ^b	ADP ^c	ADP % ^d
No.	No.	No.	Percentage, (95% CI)

ITT	PLCO 2017 ⁶	77,445	283	98	77	79 (69-86)
	SCORE 2011 ³	17,136	55	18	15	83 (59-96)
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Confronto tra diverse strategie di screening

Figure 3. Benefits, Harms, and Burden of Colorectal Screening Strategies Over a Lifetime

A Benefit: Life-years gained per 1000 individuals screened

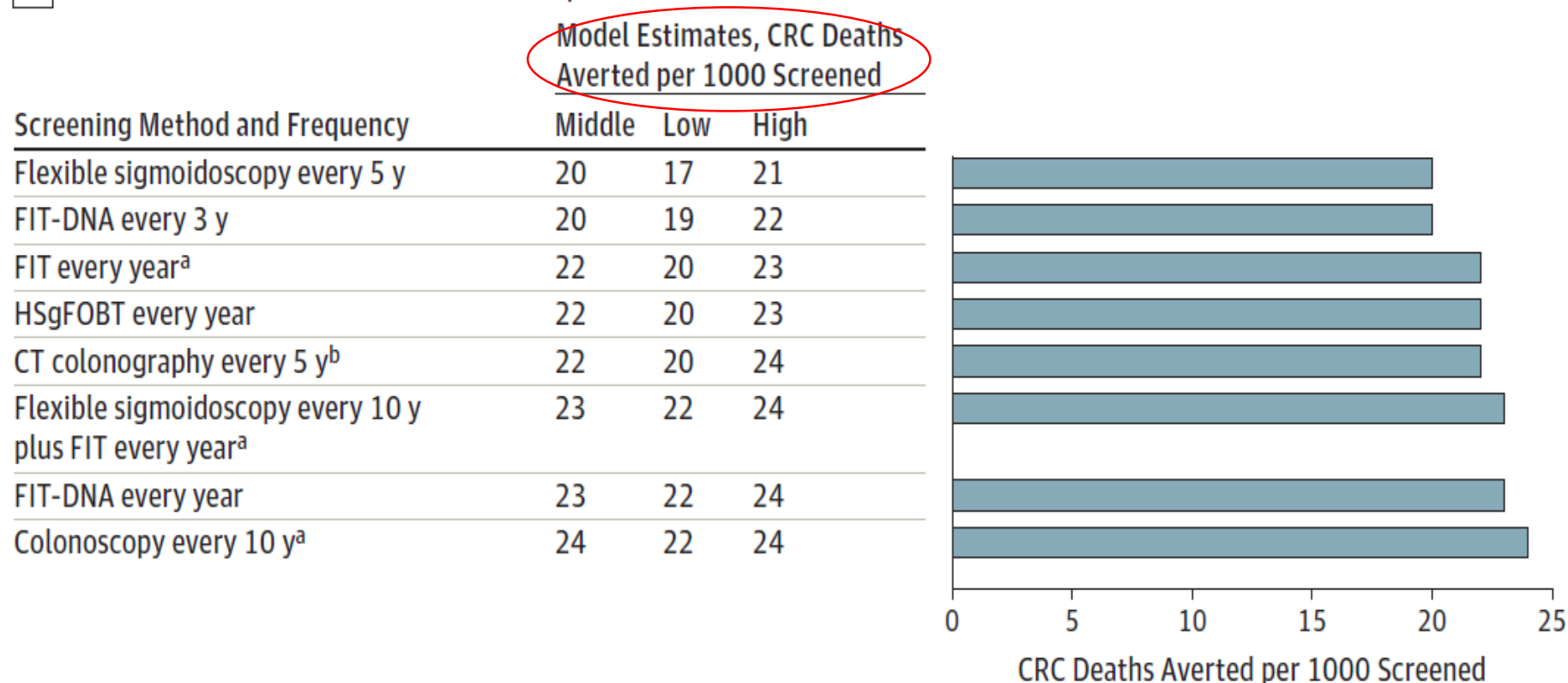


USPSTF Recommendation Statement: Screening for Colorectal Cancer

JAMA June 21, 2016 Volume 315, Number 23

Figure 3. Benefits, Harms, and Burden of Colorectal Screening Strategies Over a Lifetime

B Benefit: Colorectal cancer deaths averted per 1000 individuals screened



USPSTF Recommendation Statement: Screening for Colorectal Cancer

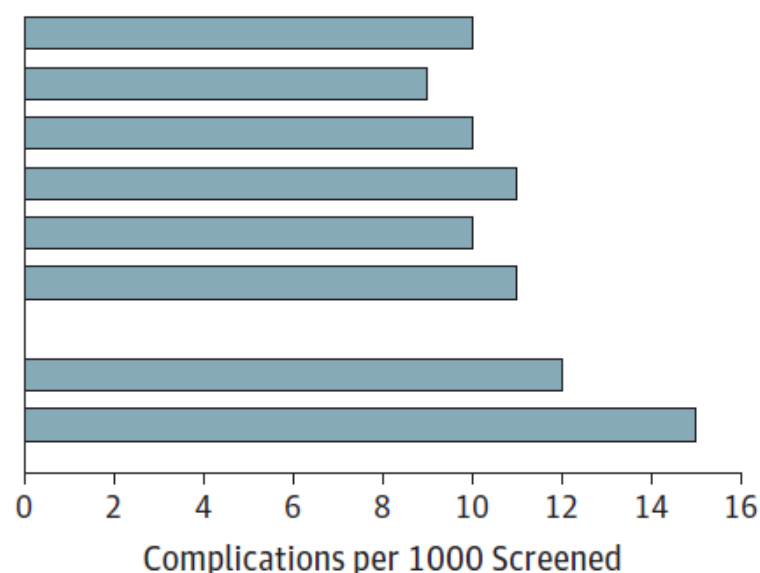
JAMA June 21, 2016 Volume 315, Number 23

Figure 3. Benefits, Harms, and Burden of Colorectal Screening Strategies Over a Lifetime

C Harms: Complications (gastrointestinal and cardiovascular events) of colorectal cancer screening and follow-up testing per 1000 individuals screened^c

Model Estimates, Complications
per 1000 Screened

Screening Method and Frequency	Middle	Low	High
Flexible sigmoidoscopy every 5 y	10	9	12
FIT-DNA every 3 y	9	9	10
FIT every year ^a	10	10	11
HSgFOBT every year	11	11	11
CT colonography every 5 y ^b	10	10	11
Flexible sigmoidoscopy every 10 y plus FIT every year ^a	11	11	12
FIT-DNA every year	12	12	13
Colonoscopy every 10 y ^a	15	14	15

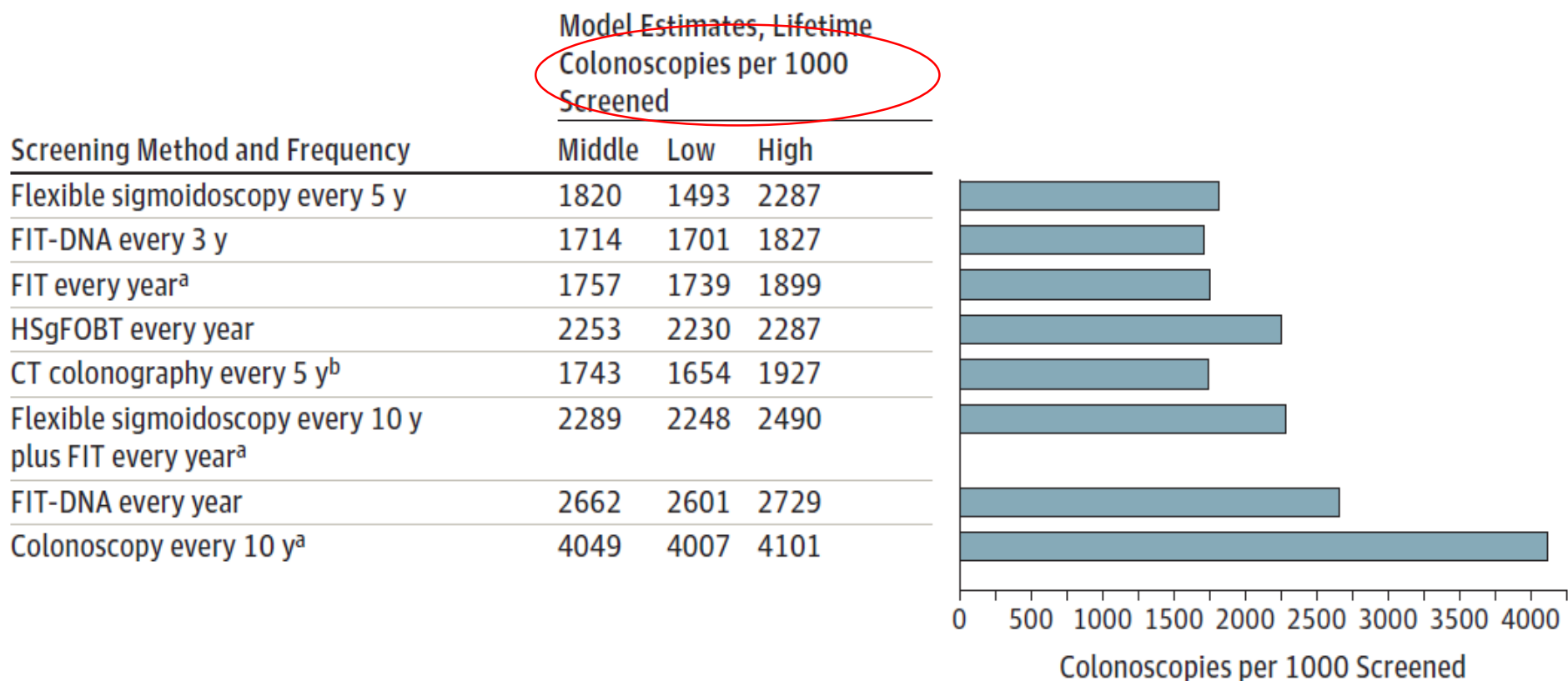


USPSTF Recommendation Statement: Screening for Colorectal Cancer

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Figure 3. Benefits, Harms, and Burden of Colorectal Screening Strategies Over a Lifetime

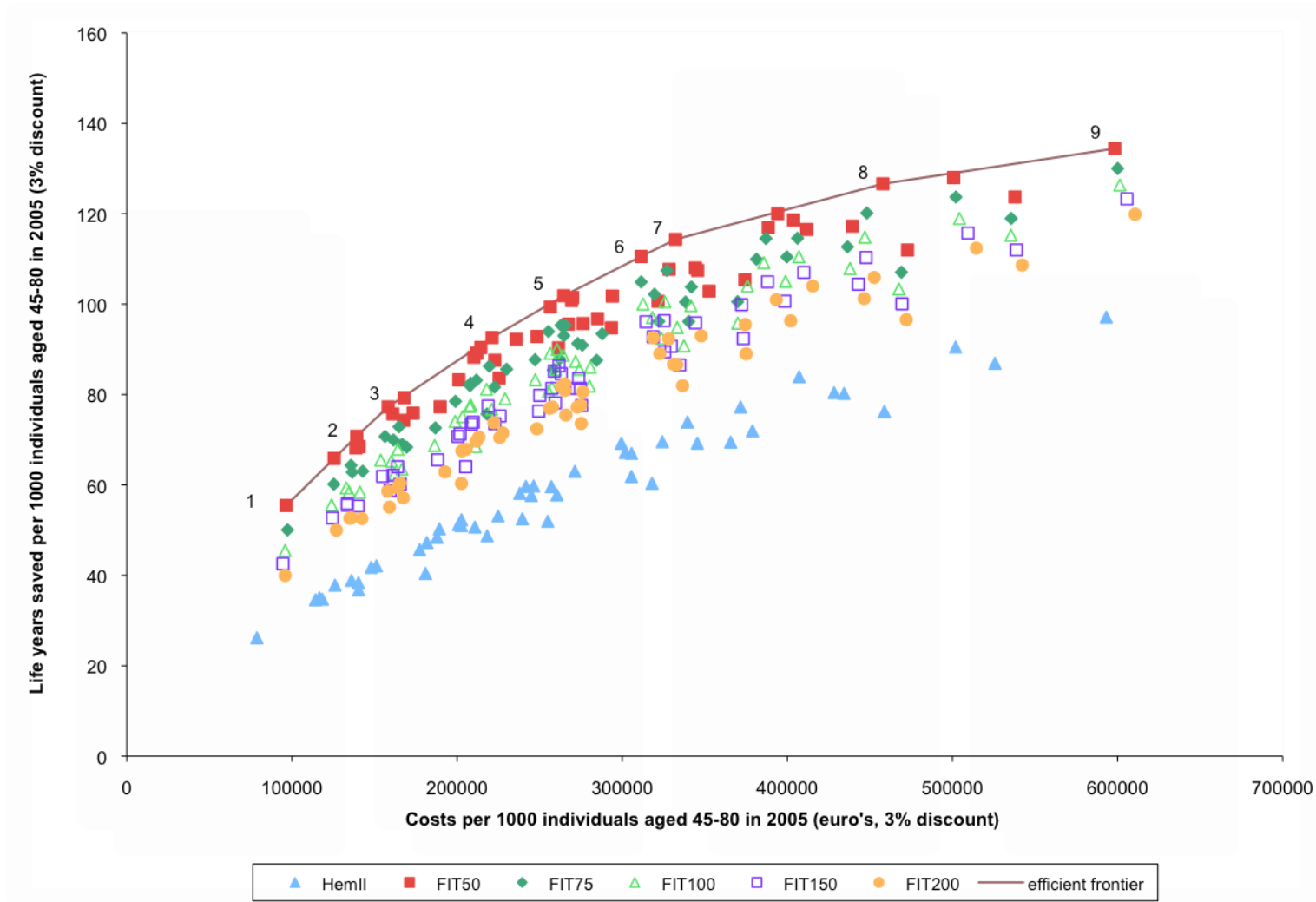
D Burden: Lifetime No. of colonoscopies per 1000 individuals screened



USPSTF Recommendation Statement: Screening for Colorectal Cancer

JAMA June 21, 2016 Volume 315, Number 23

Cost – performance modelling of gFOBt and FIT



Strategie alternative o complementari

- Prevenzione primaria e screening: es polmone,colon,mammella
- Screening organizzato e spontaneo: mutazioni germinali, intervalli lunghi tra due test
- Contesto di erogazione dell'intervento: fattibilità, adesione, risorse
- Bilancia vantaggi svantaggi
- Costo per DALY's prevenuto

Nuove tecnologie di screening: criteri per
l'introduzione a livello di popolazione

Le 5 fasi di ricerca per lo sviluppo di biomarcatori

<i>Preclinical Exploratory</i>	PHASE 1	<i>Promising directions identified</i>
<i>Clinical Assay and Validation</i>	PHASE 2	<i>Clinical assay detects established disease</i>
<i>Retrospective Longitudinal</i>	PHASE 3	<i>Biomarker detects disease early before it becomes clinical and a "screen positive" rule is defined</i>
<i>Prospective Screening</i>	PHASE 4	<i>Extent and characteristics of disease detected by the test and the false referral rate are identified</i>
<i>Cancer Control</i>	PHASE 5	<i>Impact of screening on reducing the burden of disease on the population is quantified</i>

Keynote review: Recent advances in biomarkers for cancer diagnosis and treatment

Reviews • KEYNOTE REVIEW

Upender Manne, Rashmi-Gopal Srivastava and Sudhir Srivastava

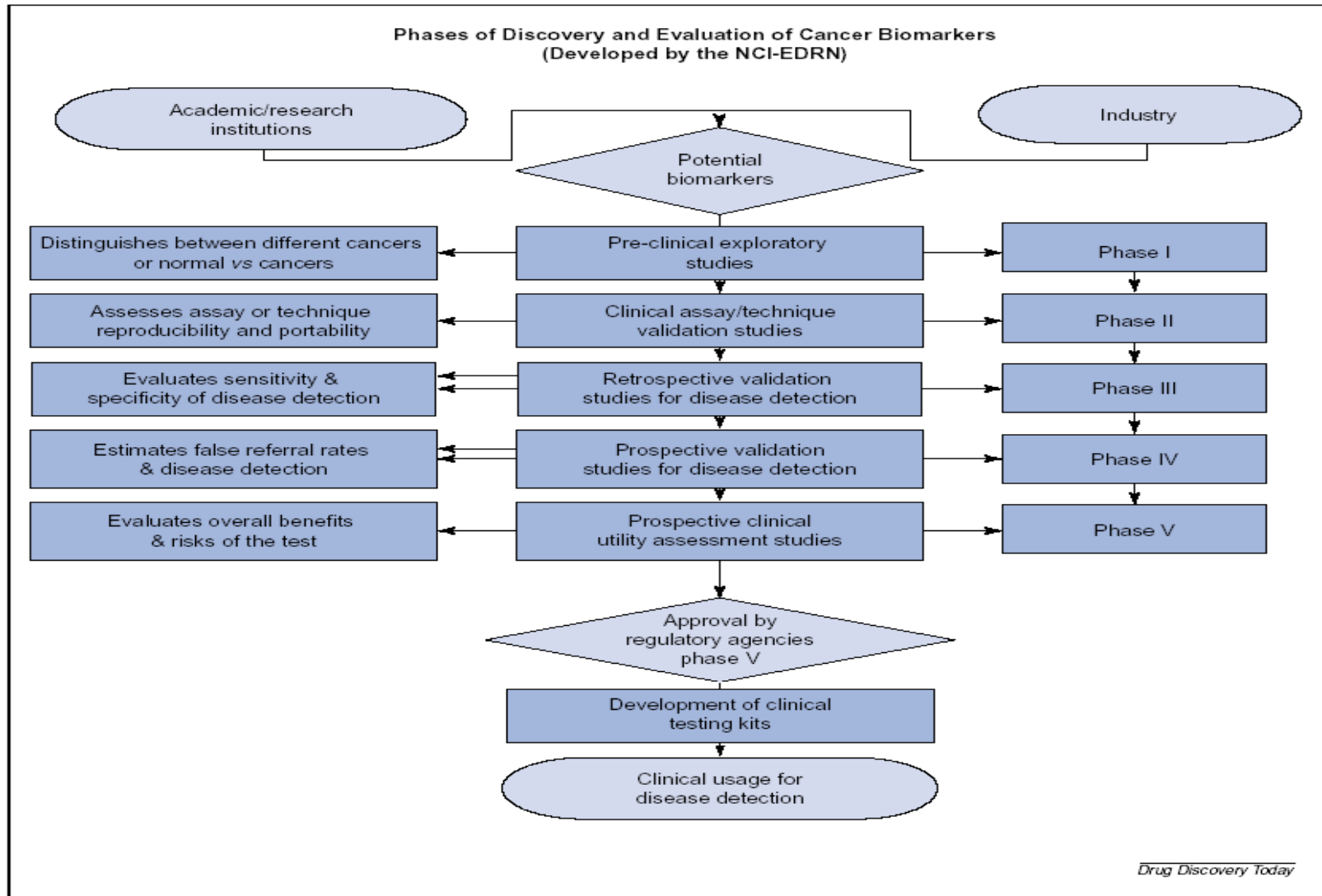


FIGURE 1

Phases of cancer biomarker development and validation. Approval by regulatory agencies will vary by the country-specific regulations and may commence after the completion of Phase III trials for limited use.

Table 2**Candidate Luminex xMAP® Lung Cancer Serum Biomarkers (N=70)**

Biological Group	Protein Analytes	Assay Source
Cytokines	IL-6, IL-8, TNF α , TNF-RI, TNF-RII, G-CSF G-CSF-R, M-CSF, IL-2R, IL-6R, IL-1RT1 sCD40-L, GRO α	Invitrogen/Biosource, Camarillo, CA Bio-Rad Laboratories, Hercules, CA
Chemokines	CCL5 (RANTES), MCP-1,3; eotaxin, LIF, MIF, IP-10	Invitrogen/Biosource Bio-Rad Laboratories
Growth/angiogenic factors	EGF, VEGF, BFGF, EGFR, c-ErbB-2, IGFBP-1 angiostatin, THBS1, HGF, NGF, PDGF, SCGF-B SDF-1 α , SCF	Invitrogen/Biosource Bio-Rad Laboratories UPCI LPL
Cancer antigens	CEA, AFP, CA 72-4, TTR, HE4, SCC	UPCI LPL
Apoptotic proteins	Cyfra 21.1, TRAIL, sDR5, sFas, sFasL	UPCI LPL
Proteases	Kallikrein 10, MMP-1,7,8,9,12	UPCI LPL R&D Systems, Minneapolis, MN
Adhesion molecules	sICAM-1, sVCAM-1, E-selectin	Millipore/Linco, St. Louis, MO
Hormones	PRL, TSH, LH, ACTH, GH, FSH	Millipore/Linco
Adipokines	Adiponectin, leptin, resistin	Millipore/Linco
Other biomarkers	Mesothelin, Hsp70, ULBP-1,2, MICA, SAA PAI-1 (SERPINE1), MPO, thrombospondin-1, ULBP-1,2	UPCI LPL Millipore/Linco

Table 1. List of standard and protocols developed by EDRN.^a

Assays	Applications
Validation of bleomycin-induced chromosomal breakage in lymphocytes	Biomarker of lung cancer susceptibility
Validation of 3.4-kb mitochondrial DNA deletion	Biomarker for prostate cancer risk
Development of high-density breast and prostate tissue microarrays	Testing of in situ hybridization and other molecular probes
Validation of SOPs ^b for microsatellite instability and DNA methylation assays	Biomarkers for bladder cancer
Validation of saliva-based mRNA assay	Biomarkers of oral cancer
Validation of proteomic prostate-specific biomarkers, including percent proPSA and other PSA isoforms	Biomarkers for improving PSA screening of prostate cancer
Urine PCA3 assay	Detection of prostate cancer
Urine/TMA assay for T2S:ERG fusion	Detection of prostate cancer
FISH assay for T2S:ERG fusion	Detection of prostate cancer
Aptamer-based assay	Detection of lung cancer
Proteomic panel for Lung Cancer	Detection of lung cancer
OVA1 TM test for ovarian cancer	Differential diagnosis of benign pelvic mass from ovarian cancer
ROMA for ovarian cancer	Differential diagnosis of benign pelvic mass from ovarian cancer
Vimentin methylation in stool	Detection of colon cancer
SOPs for blood, sera, plasma, urine, stool	Standard reference sample sets
8-oxyguanine DNA glycosylase (8OGG); alkyl-adenine DNA glycosylase; APE1 endonuclease	Measuring DNA repair capacity for lung cancer risk

^a Retrieved from the EDRN 5th report [NCI (3)].

^b SOP, standard operating procedure; PCA, prostate cancer; TMA, transcription-mediated amplification; ERG, v-ets erythroblastosis Virus E26 oncogene homolog; FISH, fluorescence in-situ hybridization; ROMA, risk of ovarian malignancy algorithm; APE1, apurinic endonuclease 1.

Table 2. Adoption of EDRN-supported assays.^a

Detection/biomarker assay	Clinical translation validation
Blood	
proPSA	FDA ^b IVD pending review
Urine	
PCA3	FDA cleared
Urine/TMA assay for T2S:ERG fusion for PCA	CLIA in process
FISH for T2S:ERG fusion for prostate cancer	In CLIA Lab
Aptamer-based markers for lung cancer	In CLIA Lab
Proteomic panel for lung cancer	In CLIA Lab
OVA1 TM for ovarian cancer	FDA cleared
SOPs for blood (serum, plasma), urine, stool	Frequently used by biomarker research community
Vimentin methylation marker for colon cancer	In CLIA Lab
ROMA algorithm for CA125 and HE4 tests for pelvic mass malignancies	FDA cleared
Blood/DCP and AFP-L3 for HCC	FDA cleared
Blood GP73 for HCC	Together with AFP-L3 used in China for monitoring/risk assessment of cirrhotic patients for HCC

^a Retrieved from the EDRN 5th report [NCI (3)].

^b FDA, US Food and Drug Administration; IVD, in vitro diagnostic. For other abbreviations see the text and the Table 1 footnote.

Table 3. Candidate biomarkers tested for early detection of ovarian cancer.

Marker	Diagnostic sensitivity at 95%, diagnostic specificity (95% CI)
CA125	0.73 (0.64–0.84)
HE4	0.57 (0.50–0.70)
Transthyretin	0.47 (0.38–0.56)
CA15.3	0.46 (0.39–0.54)
CA72.4	0.40 (0.33–0.52)
IGFBP2 ^a	0.38 (0.30–0.45)
Cytokeratin 19	0.37 (0.25–0.45)
IGF2	0.36 (0.28–0.49)
Kallikrein 6	0.36 (0.26–0.43)
Mesothelin	0.35 (0.27–0.46)
B7-H4	0.35 (0.27–0.42)
Apolipoprotein A1	0.34 (0.26–0.43)
sV-CAM	0.34 (0.22–0.42)
Prolactin	0.34 (0.15–0.49)
Chitinase	0.31 (0.23–0.38)
Spondin-2	0.28 (0.18–0.36)
MIC1	0.24 (0.14–0.30)
CA19.9	0.23 (0.18–0.30)

Transferrin	0.23 (0.15–0.32)
IGFBP1	0.21 (0.15–0.31)
Hepcidin	0.21 (0.12–0.28)
TSH	0.19 (0.13–0.25)
CTAP-III	0.19 (0.12–0.24)
MMP3	0.17 (0.11–0.27)
MMP2	0.17 (0.08–0.28)
GH	0.16 (0.10–0.23)
MIF	0.15 (0.09–0.24)
Eotaxin	0.15 (0.07–0.23)
MPO	0.14 (0.09–0.22)
EGFR	0.10 (0.05–0.17)
ITIH4	0.09 (0.05–0.16)
B2M	0.05 (0.02–0.12)

^a IGFBP2, insulin-like growth factor binding protein-2; IGF2, insulin-like growth factor-2; sV-CAM, Soluble vascular cell adhesion molecule; MIC1, macrophage inhibitory cytokine 1; TSH, thyroid stimulating hormone; CTAP-III, connective tissue activating peptide-III; MMP3, matrix metallo-proteinase-3; GH, growth hormone; MIF, macrophage migration inhibitory factor; MPO, myeloperoxidase; EGFR, epidermal growth factor receptor; ITIH4, inter-alpha-trypsin inhibitor heavy chain family, member 4; B2M, β -2 microglobulin.

Commento

- Sviluppare e adottare DALY's come outcome per stimare l'impatto degli screening:
 - i DALY's comprendono sia gli anni di vita persi per morte precoce che gli anni di vita vissuti con disabilità
 - Permettono confronti tra diversi programmi, protocolli e test. I costi dei DALYs sono quantificabili.

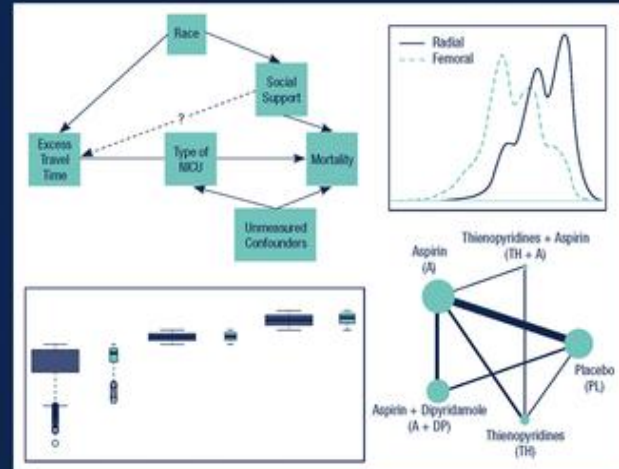
Commento

- Comparative effectiveness research

Comparative effectiveness research (CER) is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care (IOM 2009).

Chapman & Hall/CRC Biostatistics Series

Methods in Comparative Effectiveness Research



Edited by
Constantine Gatsonis
Sally C. Morton



CRC Press
Taylor & Francis Group

A CHAPMAN & HALL BOOK

- Grazie per l'attenzione